The University of Chicago

THE STERIC INHIBITION OF RESONANCE

A DISSERTATION SUBMITTED TO THE FACULTY
OF THE DIVISION OF THE PHYSICAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF DOCTOR
OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY
JUNE, 1940

By
WILLIAM CARL SPITZER

CHICAGO, ILLINOIS
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INTRODUCTION

The work presented in this thesis was undertaken in order to investigate the inhibition by ortho substituents of resonance in aromatic nitro-compounds and aromatic nitriles. Few papers dealing with such an effect in the nitro-compounds have appeared in the literature, while the investigation of the nitriles from this point of view has been entirely neglected. Other types of compounds, chiefly aromatic amines, have been more thoroughly studied, and a large amount of supporting evidence for such an inhibiting effect has been adduced. The results of some of the more important researches will be reviewed in another section of this paper.

The derivation of the theory of resonance from quantum mechanics and the interpretation of the theory in terms of molecular structure are fully treated in textbooks on the subject,[1] but the main features of the theory as applied to molecular structure may be reviewed briefly. If the structure of a molecule can be written in several ways which differ only in the arrangement of electrons about the atomic nuclei, whose relative positions remain fixed, then the molecule is said to resonate between the various structures. This phenomenon is not to be construed as a form of tautomerism, for the resonance "hybrid" does not behave like an equilibrium mixture of several compounds. On the contrary, the resonance hybrid has a single structure, which is intermediate between those of the several structures under consideration. Its properties may, in fact, be quite different from those of any contributory structure. A familiar example of this is benzene, which is considered to resonate between the two Kekulé and the three Dewar structures, although benzene has the properties of neither the ethylenic type Kekulé structures nor the para-bonded Dewar formulae.

The energy content of the resonance hybrid is lower than

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[1] Pauling and Wilson, "Introduction to Quantum Mechanics," New York, McGraw-Hill, 1935. Pauling, "The Nature of the Chemical Bond," Cornell University Press, 1939.

that of any contributory structure and the stability is correspondingly higher. This lower energy is manifested in lower heats of hydrogenation[2] and of combustion[3] than those calculated from data obtained from compounds which cannot resonate. The difference is attributed to resonance energy and represents a stabilization of the molecule to that extent.

The electrical charge distribution in a resonating molecule is intermediate between those of the contributory structures and, as a result, the dipole moment differs in magnitude from that calculated from individual bond moments in the classical structure. In 1931, in an investigation of the dipole moments of saturated and unsaturated compounds which contained identical substituent groups, Sutton correlated the differences between the moments of aromatic and tertiary aliphatic compounds with the directive influences of the substituents in aromatic nuclei.[4] Sutton suggested that simple electronic shifts could so alter the charge distribution within the molecule that the magnitude of the dipole moment would be changed from the value calculated from individual bond moments. This theory was extended to the explanation of the abnormal dipole moment of nitrobenzene (3.95 D) as compared with that of aliphatic nitro-compounds (about 3.1 D). Likewise an explanation was offered for the large dipole moment of aniline (1.53 D) as compared with the moments of aliphatic amines (1.2 to 1.4 D). It was suggested that this phenomenon was due to a quantum mechanical resonance among several different structures.[5]

Molecules such as nitrobromobenzene, nitrobenzene, aniline, phenol, and nitroaniline are considered as resonance hybrids between the classical structures and structures of the following types:

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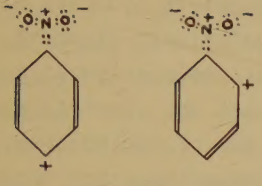
[2]Conant and Kistiakowsky, Chem. Rev., 20, 181 (1937).

[3]Pauling and Sherman, J. Chem. Phys., 1, 606 (1933).

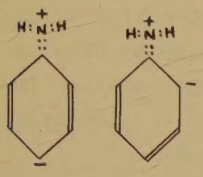
[4]Sutton, Proc. Roy. Soc., 133A, 668 (1931).

[5]Sutton, Trans. Far. Soc. 30, 789 (1934); Kumler and Porter, J. Am. Chem. Soc., 56, 2549 (1934); Ingold, Chem. Rev., 15, 225 (1934).

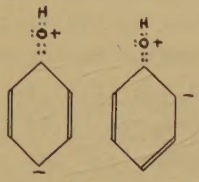


NITROBENZENE

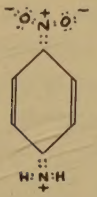
NITROBROMOBENZENE



ANILINE



PHENOL



NITROANILINE

An examination of the formal charges in structures of these types shows how these structures explain the deviation of the dipole moments from those of aliphatic compounds for which similar structures cannot be written.

The molecule is not to be considered as oscillating between these structures and the normal one, but as intermediate in structure and partaking of the characteristics of each. The consideration of what structures are important in the resonance hybrid is guided by the stability of the particular electrical charge distribution which would exist in each structure in question. Thus meta-quinoid formulae, although they can be written, involve highly unstable electronic arrangements, inasmuch as the long meta-bond must be employed. Consequently such structures may be safely neglected. Furthermore, structures involving valence shells of more than eight electrons for atoms of the first row of the periodic system are omitted, since such arrangements are unknown. Even for elements of higher rows, where compounds such as sulfur hexafluoride are known, it is usually possible to write resonating structures in which the octet rule is not violated.

The formal charges residing in structures such as those depicted above suggest a charge distribution which would explain the deviation of the dipole moment from that calculated on the basis of the classical structure. These charges would cause a secondary moment, which is called a mesomeric moment (or interaction moment, to denote interaction between the nucleus and substi-

tuent) and which has vector properties like those of ordinary moments. These effects are especially marked in the para-disubstituted benzenes, where the mesomeric effects of two para-substituents may reinforce or oppose each other, so that the electric moment of the molecule is not always the vector sum of the moments of the two mono-substituted derivatives. Extreme cases are those where the resonance effects of each group give rise to mesomeric moments in the same direction, as typified by p-nitroaniline. As pointed out by Marsden and Sutton and by Birtles and Hampson,[6] the moment of p-nitrodimethylaniline (6.87 D) is much greater than the sum of the moments of nitrobenzene (3.95 D) and of dimethylaniline (1.58 D) even though the moments are not collinear.

Now, if structures such as those pictured above are to be of importance in the resonance hybrid, there must be a tendency for the oxygen atoms of the nitro-group, for the hydrogen atoms of amino- and hydroxy groups, and for alkyl groups of alkylamino- and alkoxy-groups to be drawn into the plane of the nucleus, with consequent attainment of a coplanar configuration. Conversely, if some condition so interfered as to prevent coplanarity, then the quinoid structures would be less important in the resonance and the properties would be changed toward those represented by the classical structure. In particular, the charge distribution would be restored toward normal and the mesomeric moment would decrease in magnitude. From the spatial relationships existing in ortho substituted benzene derivatives, it can be seen that one or two fairly large ortho substituents should have precisely this effect. This was observed experimentally by Birtles and Hampson[7] and by Ingham and Hampson.[8] It was predicted that while the electric moment of a para disubstituted benzene frequently deviates widely from the vector sum of the moments of the two mono-substituted benzenes, the effect of ortho substituents as in the corresponding disubstituted durenes would be to decrease the mesomeric moment and to make the observed moment approximate the vector sum more closely. The calculated moment of nitroaminodurene is less than 4.78D, since nitrodurene has the moment 3.39D, aminodurene 1.39D, and the moments are not collinear. The observed moment is 4.98D

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[6]Marsden and Sutton, J. Chem. Soc., 1936, 599; Birtles and Hampson, ibid., 1937, 10.

[7]Ibid.

[8]Ingham and Hampson, J. Chem. Soc., 1939, 981.

larger by 0.20 D than the arithmetic sum. However, the moment of p-nitroaniline (6.10D) exceeds by 0.62D the arithmetic sum of the moments of nitrobenzene (3.95D) and of aniline (1.53D). This indicates that the mesomeric moment of p-nitroaniline has been lowered considerably by the ortho substituents. Similar results have been obtained for amino-, aminobromo-, nitro-, and nitrobromodurenes, as well as for a few durenols and durenol ethers.

REVIEW OF IMPORTANT CHEMICAL RESEARCHES

The chemical effects of ortho substituents have been recognized for many years and have been investigated most extensively in the case of aniline derivatives. Only in the past two years, however, have chemical data appeared which approach those of Hampson and his co-workers in clarity and in direct application to the theory of steric hindrance of resonance. The electrical charge distribution represented by the formal charges in the mesomeric structures of aniline is such that the ortho and para positions are especially subject to attack by reagents which act at relatively electronegative centers in the molecule. Among such reagents are nitrous and nitric acids, diazonium salts, aldehydes, and hydrogen and deuterium ions. If the steric effects of ortho substituents in inhibiting resonance cause the charge distribution to approximate more closely that of benzene, which is relatively inert, then the reactions of the substituted aniline will decrease in velocity or fail completely.

This diminished reactivity is still more characteristic for tertiary aromatic amines.[9] The comparatively large tertiary amino-group can be more effectively blocked by ortho substituents. Dimethylaniline and dimethyl-m-toluidine react readily with nitrous and nitric acids, diazonium salts, and aldehydes. However, dimethyl-o-toluidine does not react with these reagents.[10] Only a more reactive diazonium salt, such as that derived from p-nitroaniline, will couple. If a methyl, methoxyl, chloro- or nitro-group is an ortho substituent in dimethylaniline, the reactions proceed slowly or fail completely. Dimethyl-sym.-m-xylidine reacts

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[9] Gnehm and Blumer, Ann., 304, 87 (1899); Anschutz, Z. angew. Chem., 41, 691 (1928).

[10] Wurster and Riedel, Ber., 12, 1796 (1879); Weinberg, ibid., 25, 1610 (1892).

readily to give nitroso derivatives, while dimethyl-p-xylidine and dimethyl-vic.-m-xylidine are inert.

The effectiveness of ortho substituents which differ in size has been compared by von Braun in an investigation of the condensations of dimethylanilines with formaldehyde to give dimethylaminobenzyl alcohols.[11] Under identical conditions and in identical reaction times, dimethyl-o-anisidine reacted to the extent of 60%, o-chlorodimethylaniline 36%, and dimethyl-o-toluidine only 6%. All unreacted materials were recovered and the percentage reaction actually was an indirect measure of the velocity of reaction. The comparatively great reactivity of the anisidine derivative, as well as the relatively small effect of a methoxyl group in general in inhibiting reactions, can be ascribed to a possible trans-configuration of the methoxyl group with respect to the main functional and directive group.

Dimethylaniline readily exchanges the ortho and para hydrogen atoms in an acid catalyzed exchange reaction with deuterium ion. However, o-nitrodimethylaniline fails to exchange. This lack of reactivity has been correlated with the hindrance to coplanarity by the ortho nitro-group,[12] but it may also involve an inductive effect of the ortho substituent. The influence of the size of the ortho group upon the effectiveness of steric inhibition was tested by Brown, Widiger, and Letang,[13] who studied the hydrogen exchanges of o-bromo-, o-chloro-, and o-fluoro-dimethylanilines and found bromine most effective and fluorine least. The same authors also prevented coplanarity by the device of incorporating the amino-group in a puckered seven-membered ring, and then compared the hydrogen exchange with that of similar bicyclic compounds in which the nitrogenous ring was necessarily coplanar with the benzenoid ring. The order of decreasing reactivity was found to be N-methylindoline (I), N-methyltetrahydroquinoline (II), and N-methyl-homo-tetrahydroquinoline (III).

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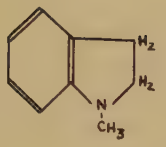
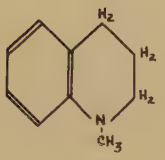
[11] v. Braun, Ber., 49, 1101 (1916); 51, 282 (1918).

[12] Brown, Kharasch, and Sprowls, J. Org. Chem., 4, 442 (1939).

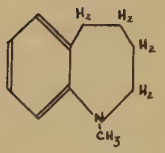
[13] Brown, Widiger, and Letang, J. Am. Chem. Soc., 61, 2597 (1939).



I



II



III

Further evidence was presented by Michaelis and his colleagues,[14] who studied the stability of Wurster's salts. These univalent products of the oxidation of aromatic p-diamines are free radicals which are stabilized by resonance among structures of the following types, in which the unpaired electron is represented by a small circle:

It was demonstrated that all Wurster's salts in which the alkylamino-groups have ortho substituents are less stable than those containing no ortho groups. These results agree with the hypothesis that the more stable salts are partially quinoid in character and are stabilized by resonance, while the instability of the compounds containing ortho substituents is due to the steric effects of these groups in inhibiting resonance.

Much less work has been done with nitro-compounds. Observations have been numerous, but the work of Hampson and his colleagues on dipole moments remains the clearest evidence for the theory of steric inhibition of resonance. The problem of resonance of nitro-compounds is closely linked with the problem of activation by the nitro-group, and in this guise the resonance theory has re-

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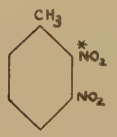
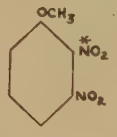
[14] Michaelis, Schubert, and Granick, J. Am. Chem. Soc., 61, 1981 (1939).

ceived considerable attention. The mesomeric structures of nitrobenzene and its derivatives have charge distributions which should make the ortho and para positions favored points of attack by reagents which act at centers of positive charge. Such reagents include ammonia, amines, hydroxide ion, and alkoxide ions. Reactions of ortho and para substituted nitrobenzenes with these reagents very often result in the replacement of the ortho or para substituent by a new group derived from the reagent. This phenomenon of activation is thus closely related to the phenomenon of resonance in the nitro-compounds.

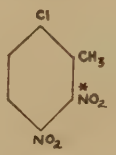
Some interesting work has been performed in the study of the reactions of certain dinitro-compounds with sodium methoxide to give nitro-anisoles and with ammonia and amines to give nitro-anilines. In the following list of compounds, the starred groups were found to be labile and to be replaced by methoxyl, amino- or alkylamino-groups, depending upon the reagent employed. The reagent and the investigator are given in each case:



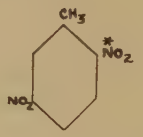
NH_3[15]



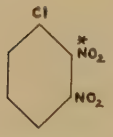
alc. NH_3[16]



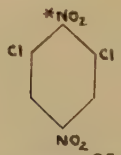
alc. NH_3[17]
alc. CH_3NH_2[18]



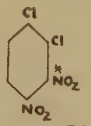
alc. NH_3[19]



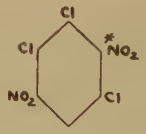
$NaOCH_3$[20]



$NaOCH_3$[21]



$NaOCH_3$[22]



$NaOCH_3$[23]

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[15]Burton and Kenner, J. Chem. Soc., 119, 1047 (1921).

[16]Bantlin, Ber., 11, 2099 (1878).

[17]Morgan and Drew, J. Chem. Soc., 117, 784 (1920).

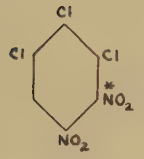
[18]Morgan and Jones, ibid., 119, 187 (1921).

[19]Kenner and Parkin, ibid., 117, 852 (1920).

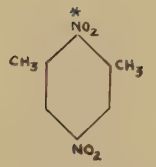
[20]Hollemann et al., Rec. trav. chim., 39, 435 (1920).

[21]Ibid. [22]Ibid.

[23]Ibid., 40, 451 (1921).



$NaOCH_3$[24]



alc. NH_3[25]

In every instance, a nitro-group located between two ortho-substituents is replaced by metathesis with the reagent. Each nitro-group in the molecule tends to activate the other nitro-group, and, according to theory, the more powerful activator should be the group which is better able to resonate, i.e. which is less inhibited sterically. An obvious conclusion is that two ortho substituents more effectively hinder coplanarity than does one. Hence the nitro-group with only one ortho substituent will be more effective in activating the group ortho or para to it.

It is of interest to note that in studying the last compound in the list and in discussing the activating influence of the nitro-group, Ibbotson and Kenner[26] postulated that at some time during the reaction the compound assumed a quinoid structure. However their theory did not closely correspond with the present theory.

The cumulative influence of many activating groups may overbalance the deactivating effects of ortho substituents and result in the replacement of one group when another course of reaction might conceivably be predicted. This is true in 2,4,5-trinitro-m-xylene, where the 5-nitro-group is replaced, although the steric factors might tend to make predictions hazardous.[27] This is in accord with the premise that resonance with quinoid structures is not necessarily completely hindered by ortho substituents, but may exist to a lesser degree, just as a twisted ethylenic double bond may exist, albeit in a highly unstable state. This

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[24] Ibid.

[25] Ibbotson and Kenner, J. Chem. Soc., 123, 1260 (1923).

[26] Ibid.

[27] Blanksma, Rec. trav. chim., 25, 168 (1916); cf. Ibbotson and Kenner, loc. cit.

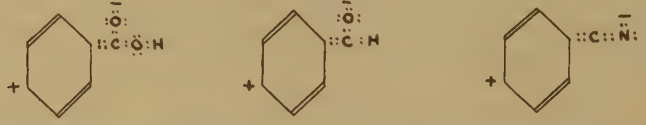
idea has already been stated by Birtles and Hampson, but not in so direct a manner.

Another example of steric inhibition, in a far different reaction is in the aldol-like condensations of aldehydes with compounds related to ortho and para nitrotoluenes. Nitrotoluene can resonate with structures of the following types:

Benzaldehyde reacts to give a benzylidene derivative with 4,6-dinitro-m-xylene, in which each nitro-group is hindered by one methyl group. Di- and tri-nitromesitylene and tri-nitropseudocumene fail to react. In these compounds, resonance of the type pictured is more completely hindered than in the xylene derivative.[28]

Good evidence has been drawn from an investigation by Wheland and Danish of the acid strengths of tris-(4-nitro-3,5-dimethylphenyl)-methane and tris-(4-nitrophenyl)-methane.[29] The latter compound displays acidity which may be ascribed to the stability of the negative ion. This stability is postulated to be the result of resonance between the normal structure and an extremely large number of quinoid structures such as those illustrated for the mesomeric ionic structures of nitrotoluene. This resonance was diminished by placing methyl groups in the ortho positions about the nitro-groups. As a consequence, tris-(4-nitro-3,5-dimethylphenyl)-methane exhibited a lower acid strength than did the simple trinitrotriphenylmethane.

The carboxyl, aldehydo-, and cyano-groups can be considered as resonating between the normal structures and structures of the following types:



The activating effects of these groups upon ortho and para substi-

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[28]Thiele and Escale, Ber., 34, 2842 (1901); Borsche, Ann., 386, 351 (1911).

[29]Danish, S.M. thesis, "Acid Strengths of Tri-aryl Meth-

tuents have been investigated by Schöpff and his students,[30] but the evidence is clear-cut only in the case of the carboxyl group. No work has been done with ortho substituted derivatives of compounds containing these groups.

The nitriles and nitroso-compounds offer an interesting application of the theory of steric inhibition. From the spatial relationships in these compounds, it is evident that ortho substituents should be without direct influence upon the resonance of the cylindrically symmetric groups, such as cyano- and nitroso-groups, which are coplanar with the nucleus in either the quinoid or benzenoid structure.

REACTIONS OF NITRO-ARYL AND CYANO-ARYL HALIDES

The presence of nitro-groups ortho or para to halogen atoms in the benzene ring renders the halogen atoms labile and subject to replacement by other groups. Reagents commonly employed for this purpose are aqueous hydroxides,[31] alcoholic hydroxides,[32] and alcoholic alkoxides, to give nitrophenols and nitrophenyl ethers; ammonia,[33] aliphatic amines,[34] aromatic amines,[35] and piperidine,[36]

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anes," Department of Chemistry, University of Chicago, 1939. Wheland and Danish, J. Am. Chem. Soc., 62, 1125 (1940).

[30]Schöpff et al., Ber., 22, 900, 3281 (1889); 23, 3440, 3445, 3450 (1890); 24, 3771, 3785, 3808 (1891).

[31]Lukaschewitz and Stenberg, Chem. Zentr., 1935, II, 212; Aoyama and Nanai, J. Pharm. Soc. Japan, 55, 40 (1935); cf. Chem. Zentr., 1935, II, 2662.

[32]Heumann, Ber., 5, 912 (1872); Willgerodt, ibid., 12, 763 (1879); 14, 2632 (1881); 15, 1002 (1882); Lobry de Bruyn, Rec.trav. chim., 9, 203 (1890); Brand, J. prakt. Chem., (2), 67, 152, 160 (1903); (2), 68, 208 (1903); Rheinlander, J. Chem. Soc., 123, 3099 (1923); Aoyama and Nanai, J. Pharm. Soc. Japan, 53, 114 (1933); cf. Chem. Zentr., 1933, II, 1669.

[33]Walker and Zincke, Ber., 5, 114 (1872); Meyer and Wurster, ibid., 5, 632 (1872); Beilstein and Kurbatow, Ann., 182, 108 (1876); Wohl, Ber., 39, 1953 (1906).

[34]Menschutkin, Ber., 30, 2967 (1897); Nagornoff, J. Russ. Phys. Chem. Soc., 29, 699 (1898); cf. Chem. Zentr., 1898, I, 886; Blanksma, Rec. trav. chim., 21, 270 (1902); Perna, J. Russ. Phys. Chem. Soc., 35, 114 (1903); cf. Chem. Zentr., 1903, I, 1127; Willgerodt, Ber., 9, 977 (1876); Nietzki and Ernst, ibid., 23, 1852 (1890).

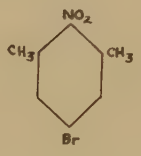
[35]Goldberg, German patent, 185, 663; Chem. Zentr., 1907, II, 957.

[36]Le Fevre and Turner, J. Chem. Soc., 1927, 1113; Brewin

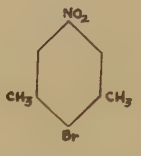
to give nitroaniline derivatives; hydrazine,[37] to give nitrophenylhydrazines; and alkali salts of acetic acid and other organic acids,[38] to give nitrophenyl esters. Less commonly used are sodiomalonic ester, sodio-acetoacetic ester,[39] metal phenoxides, thiocyanates, and sulfides.

The mesomeric structures for nitrobromobenzene indicate why the halogen atom should partake in metatheses with reagents which act at centers of low electron density. If the attainment of these quinoid structures were made more difficult by substitution of two methyl groups about the nitro-group, the reactivity of the halogen atoms toward these reagents should be greatly reduced. In order to obtain evidence for or against this prediction, the reactions of the following compounds with piperidine were investigated:

A

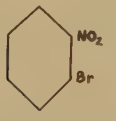


B



C

Since some further evidence might be forthcoming from the ortho series, the following were also studied:



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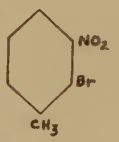

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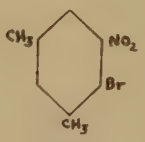
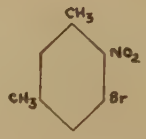


F



G

Of the reagents mentioned above, piperidine seemed to have properties which would make it the most advantageous in studying the degree of halogen removal. Factors lending to this view were the convenient boiling point (106°), the high stability and basic-

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and Turner, ibid., 1928, 332; Salkind, Ber., 64, 289 (1931); Sandin and Liskear, J. Am. Chem. Soc., 57, 1304 (1935).

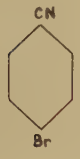
[37] Allen, J. Am. Chem. Soc., 52, 2957 (1930).

[38] Kym, Ber., 32, 3539 (1899); Borsche, ibid., 50, 1339 (1917).

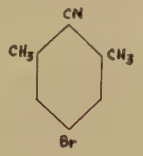
[39] Borsche, Ann. 386, 356 (1912); 402, 81 (1914).

ity, and the ability to react without the formation of side products, as pointed out by Sandin and Liskear.[40]

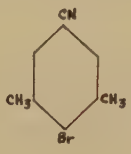
In order to determine the extent of aminolysis of the cyano-aryl halides, a rather similar but less complete series of compounds were investigated in the reaction with piperidine:



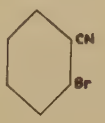
H



J



K



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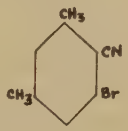

M

The reaction of piperidine with cyano-aryl halides had not been investigated and some exploratory work was necessary. It was found that the reaction resulted in the formation of p-piperidinobenzonitriles and piperidine hydrobromide and occurred without the formation of noticeable quantities of side products, so that it could be used to advantage in a quantitative study of the extent of reaction. This phase of the problem is treated more fully in the experimental part.

At the outset, it was found that the presence of two methyl groups in the positions ortho to the bromine atom reduced the reactivity of the molecule to a surprisingly low value. This result was contrary to expectation and made predictions difficult. The extremely low reactivity of such compounds was attributed in large measure to the steric effect of the methyl groups in preventing the rather large piperidine molecule from approaching the point of attack, i.e. the carbon atom to which the bromine atom is attached.

Accordingly, a search was made for another reagent, for which the hindering effect of the ortho substituents about the bromine atom would be much smaller. It was hoped that by this device a clearer set of results would be obtained. Ibbotson and Kenner[41] had found that 2,5-dinitro-m-xylene reacted with ammonia in methyl alcohol to give 5-nitro-vic.-m-xylidine, a reaction in which the nitro-group between two ortho-substituents was replaced in preference to the unhindered group. This suggested that the hydroxide ion would be a suitable reagent, since it is of the approximate size of the ammonia molecule, and, barring hydration,

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[40] Op. cit.

[41] Op. cit.

certainly smaller than any other reagent which could be employed. In order to avoid any complicating reactions with an alcoholic solvent, such as reduction or formation of nitroaryl ethers, the reactions were carried out in an aqueous dioxane solution of sodium hydroxide. A procedure such as that employed by Ibbotson and Kenner, involving the use of ammonia, could not be used advantageously in a kinetic study because it is probably a two-phase reaction. The reagent, moreover, would probably change during the course of the reaction from ammonia to a mixture of ammonia with secondary and tertiary amines resulting from the ammonolysis. The presence of any alcohol would undoubtedly cause the formation of ethers and reduction products.

TABLE 1

Reagent: piperidine Volume of solvent: 10 c.c.
Solvent: benzene Temperature: 85°
Time: 8 hours

Compound	Moles Compound	Moles piperidine	Per cent Reaction	Velocity Constant (kx 10^4)[a]
p-nitro-bromobenzene (A)	.001789	.05084	52.8	280[b]
	.001783	.05084	51.9	270
	.001769	.05092	54.8	280
	.001785	.05081	55.2	290
	.001793	.05093	53.4	280
	.001803	.05096	54.2	290
2-nitro-5-bromo-m-xylene (B)	.001789	.05081	2.4	7.6
	.001794	.05096	2.2	7.6
	.001782	.05098	2.0	7.6
2-bromo-5-nitro-m-xylene (C)	.001794	.05096	0.64	2.3
	.001794	.05096	0.43	1.5
	.001794	.05090	0.36	1.2
o-nitrobromo-benzene (D)[c]	.001796	.05096	82.2	5190
	.001801	.05094	81.7	5110
2-bromo-3-nitro-toluene (E)	.001802	.05097	8.3	32.6
	.001794	.05098	8.2	32.9
4-nitro-5-bromo-m-xylene (G)	.001793	.05096	12.3	48.8
	.001799	.05100	12.4	47.3
4-bromo-5-nitro-m-xylene (F)	.001801	.05101	2.4	7.6
	.001790	.05093	2.3	7.6

[a] Velocity constants were calculated on the assumption that the reaction is of second order. The units of the constants are liters per hour per mole.

[b] The velocity constant for p-nitrobromobenzene agrees fairly well with that calculated from data of Sandin and Liskear (*op. cit.*) on the same reaction. A small difference is probably due to the fact that these authors used a slightly different mol ratio of reactants, thus changing the solvent, which is actually a mixture of benzene and piperidine.

[c] The reaction time for o-nitrobromobenzene was one hour.

TABLE 2

Solvent: ethylbenzene Volume of solvent: 10 c.c.
Reagent: piperidine Temperature: 121°
Time: 8 hours

Compound	Moles Compound	Moles Piperidine	Per cent Reaction	2d-order Velocity Constant ($k \times 10^4$)
p-bromobenzonitrile (H)	.001791 .001782	.05100 .05095	13.0 12.2	50 47
4-bromo-2,6-dimethylbenzonitrile (J)	.001798 .001800	.05093 .05096	3.54 4.15	13.5 15.4
4-bromo-3,5-dimethylbenzonitrile (K)	.001800 .001798	.05094 .05096	0.13 0.13	0.1 0.1
O-bromobenzonitrile (L)	.001801 .001795	.05095 .05096	13.3 12.9	54 50
6-bromo-2,4-dimethylbenzonitrile (M)	.001800 .001801	.05097 .05092	4.64 4.43	17.6 16.8

TABLE 3

Reagent: NaOH in aq. dioxane
Volume: 65 c.c.

Compound	Moles Compound	Moles NaOH	Time in hrs.	Per cent Reaction	2d-order Velocity Constant ($k \times 10^3$)
p-nitrobromobenzene (A)	.001800 .001797	.01919 .01920	24 24	7.23 7.51	12.7 13.7
2-nitro-5-bromo-m-xylene (B)	.001802 .001800	.01921 .01921	48 48	1.95 1.71	1.5 1.2
2-bromo-5-nitro-m-xylene (C)	.001800 .001802	.01921 .01921	48 48	1.20 1.63	.85 1.2

DISCUSSION OF RESULTS

As expected, the reactivity of 2-nitro-5-bromo-m-xylene (B) toward either piperidine (Table 1) or sodium hydroxide (Table 3) was found to be much lower than that of p-nitrobromobenzene (A). This could be due to the inductive effect of the methyl groups meta to the bromine atom, or to the steric effect of the methyl groups in hindering the coplanarity of the nitro-group with the nucleus, or to a combination of both effects. Information bearing upon this point was obtained from the reactions of the corresponding nitriles (Table 2). While the presence of two methyl groups ortho to the nitro-group occasioned a 37-fold decrease in the velocity of reaction (ratio 280 : 7.6),[42] the same substituents about the cyano-group gave rise to only an approximately threefold decrease (Table 2, compounds H and J, ratio 49 : 14). Since ortho-groups cannot seriously affect the resonance in aromatic nitriles, the main factor in lowering the reaction velocity of the nitrile J must be the inductive effect of the two methyl groups meta to the bromine atom. This effect is relatively small compared with that observed in the analogous nitro-compound B, and it is entirely reasonable to attribute the major influence of the methyl groups on the reactivity of compound B to a steric effect operating to hinder the coplanarity of the nitro-group with the ring.

Corroborative evidence comes from the ortho series of compounds. From Table 2 it is seen that introduction of one methyl group ortho and one para to the nitrile group, as in compound M, reduces the reactivity by a factor of about three (ratio 52 : 17). The analogous substitutions in the nitro-compound (Table 1, compounds D and G) cause a decrease of over a hundred-fold (ratio 5150 : 48). In the nitriles, this de-activating effect can only be attributed to the inductive effect of the methyl groups upon the bromine atom situated meta to the methyl groups. This is a small effect compared with that observed in the similarly substituted nitro-compounds, and again the conclusion is inevitable that there is a very real effect of the methyl groups in inhibiting the coplanarity of an ortho-nitro-group with the nucleus.

Not much can be gained from a comparative study of com-

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[42] This and other ratios used in discussing the nitro- and cyano-compounds are ratios of the velocity constants, each multiplied by 10^4 for convenience.

pounds A and C (Table 1) as against compounds H and K (Table 2), in which the effect of substituents ortho to the bromine atom is demonstrated. It can only be remarked that the ratios of the reaction velocities in each pair are very large and indicate a large effect of ortho substitution around the bromine atom, which may be either inductive in nature or steric, in keeping the reagent from the point of attack. Some information relative to this, but the value of which is open to question, is gained from the reaction of compounds A and C with sodium hydroxide. While the ratio of the reactivities of p-nitrobromobenzene and 2-bromo-5-nitro-m-xylene toward piperidine is 165 (280 : 1.7), the ratio in the reaction with sodium hydroxide is only 13 (130 : 10), as seen from Table 3. Also, in the reaction with piperidine, 2-nitro-5-brom -m-xylene (B) reacts about four times as rapidly as 2-bromo-5-nitro-m-xylene, while in the corresponding reactions with sodium hydroxide the ratio is nearer unity (1.3 : 1). Decreasing the size of the reagent has thus diminished the effect of the methyl groups ortho to the bromine atom. If the not altogether unreasonable assumption is made that the use of a smaller reagent does not greatly affect the relative velocities, or at least not to the extent observed for compound A and C (160 : 13), then the results obtained with sodium hydroxide would indicate that the inductive effect upon the bromine atom of ortho methyl groups is not the only factor in reducing the reactivity. The data, interpreted from the point of view of this hypothesis, would indicate that the low reactivities of the compounds in which the bromine atom is located between two ortho methyl groups are in large measure due to the purely steric effect of preventing the approach of the reagent, although the inductive effect is fairly important.

The effect of a methyl group para to the bromine atom can also be estimated by comparing the reactivities of compounds D, E, and F (Table 1). While substituting a methyl group ortho to the bromine atom results in over a hundredfold decrease in reactivity (compounds D and E), an additional methyl group para to the bromine, as in compound F, causes only a further fourfold decrease (from 33 to 7.6). It was shown that two methyl groups meta to the bromine cause a threefold decrease in reactivity, and, as expected, the para group displays a slightly greater effect. If, as might be supposed, the para group has an inductive effect comparable to that of a single ortho group, then these results suggest that the

large influence of the ortho methyl group in compound E is a combination of inductive and steric effects. However, in drawing conclusions about the relative inductive effects of ortho and para methyl groups from these data, any dogmatism is unwarranted. Nevertheless, the larger inductive effect of a para methyl group as compared with that of two meta methyl groups seems clear enough.

In résumé, the following points should be emphasized as having been demonstrated:

1. In ortho and para nitro-bromo-compounds, the effect of a methyl group ortho to the nitro-group in decreasing the reactivity of the bromine atom is in large measure steric and may be interpreted as due to hindrance of resonance. However, a relatively small inductive effect upon the bromine atom also plays a part in lowering the reactivity. In the ortho nitrobromo-compounds, the steric effects are very marked.

2. The effect of methyl groups ortho to a bromine atom is a combination of inductive and steric effects, where the word steric has its classical meaning. The relative importance of these influences is difficult to estimate in this instance. The steric effects observed in the aminolysis of nitrobromo-compounds by piperidine are greater than in the hydrolysis by sodium hydroxide.

3. A methyl group para to a bromine atom has a slightly greater inductive effect than that of two methyl groups in the meta positions.

4. The effect of substituents ortho to the nitro-group as determined from the reactivities of p-nitrobromo-compounds is not as large as was expected from a consideration of the chemical data presented in the review of the literature, and particularly from a consideration of the work of Ibbotson and Kenner on 2,5-dinitro-m-xylene. However in the o-nitrobromo-compounds, the influence of ortho substituents is much larger and agrees better with the expected effect.

EXPERIMENTAL PART

Some of the compounds considered essential to this investigation were already described in the literature. Others were heretofore unknown and involved many steps in synthesis and proof of structure. The known compounds are listed in section I and the description of the methods used to obtain the new compounds is given in part II. Capital letters denote the compounds in the

tables of experimental results.

I

p-Nitrobromobenzene (A): Prepared by nitration of bromobenzene.[43] M.p. 126°. M.p. lit. 127°.

o-Nitrobromobenzene (D): Prepared from o-nitroaniline by a Sandmeyer reaction. M.p. 41.5-42.5°. M.p. lit. 41.5°.

4-Nitro-5-bromo-m-xylene (G): Obtained by diazotization of 5-bromo-6-nitro-asym.-m-xylidine in alcoholic solution.[44] M.p. 39-40°. M.p. lit. 39-40°.

2-Bromo-3-nitrotoluene (E): Prepared from 3-nitro-o-toluidine by a Sandmeyer reaction. M.p. 39-40°.

o-Bromobenzonitrile (L): Prepared from o-bromoaniline by a Sandmeyer reaction. M.p. 54-55°.

p-Bromobenzonitrile (H): The Eastman product was recrystallized from dilute alcohol. M.p. 113°. M.p. lit. 113°.

6-Bromo-2,4-dimethylbenzonitrile (M): Prepared from 5-bromo-asym.-m-xylidine[45] by the method of Wheeler and Thomas.[46] M.p. 86-87°. M.p. lit. 86-87°.

4-Bromo-5-nitro-m-xylene (F): No adequate directions for the preparation of this compound could be found. The method of Blanksma[47] was unsatisfactory and was modified as follows. Ten grams of 5-nitro-asym.-m-xylidine[48] were suspended in 40 c.c. of 18% hydrobromic acid and diazotized with 5 grams of sodium nitrite at 20°. The diazonium solution was poured into a suspension of cuprous bromide prepared by passing sulfur dioxide through a solution of 13 grams of potassium bromide, 11 grams of copper sulfate, and 30 c.c. of 36% hydrobromic acid in 55 c.c. of water. The reaction product was isolated by steam distillation and was recrystallized from 95% alcohol. M.p. 55.5-56.5°. M.p. lit. 56°.

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[43] Erdmann, "Anleitung zur Darstellung organische Präparäte."

[44] Noelting, Braun, and Thesmar, Ber., 34, 2242 (1901).

[45] Ibid.

[46] Wheeler and Thomas, J. Am. Chem. Soc., 50, 2286 (1928).

[47] Blanksma, Rec. trav. chim., 25, 165 (1906).

[48] Willgerodt and Schmierer, Ber., 38, 1472 (1905).

2-Nitro-5-bromo-m-xylene (B): This compound was synthesized by the method of Dr. G.W. Wheland, who first prepared it during the course of some unpublished work. The following method gave consistently good results. Ten grams of 5-bromo-vic.-m-xylidine, prepared by bromination of vic.-m-xylidine,[49] were dissolved in a mixture of 400 c.c. of water and 25 grams of concentrated sulfuric acid. The amine was diazotized below 5° with 5.5 grams of potassium nitrite in 10 c.c. of water. The diazonium solution was made just alkaline to litmus by the dropwise addition of concentrated aqueous sodium hydroxide, the temperature being held constant. It was then made very faintly acid by the addition of two or three drops of concentrated sulfuric acid. Cuprocuprisulfite, prepared from 20 grams of copper culfate and 16.5 grams of sodium sulfite, was then added and the mixture poured into 150 c.c. of water containing 80 grams of potassium nitrite. The mixture was heated to boiling and then steam distilled. The solid condensate was extracted from the aqueous distillate by extraction with ether and recovered from the ether by evaporation. The residue was recrystallized from 95% alcohol and was obtained in colorless needles; m.p. 65.5-66.5°. Yield, 4 grams (36% of theoretical). The compound turns yellow on long standing in light, and samples were recrystallized before use.

Analysis: Calc. for $C_8H_8O_2NBr$: C,41.74; H, 3.48; N, 6.09. Found: C, 41.83; H, 3.48; N, 6.15.

4-Bromo-2,6-dimethylbenzonitrile (J): Prepared by a Sandmeyer reaction from 5-bromo-vic.-m-xylidine. The product was isolated by steam distillation of the reaction mixture and was purified by recrystallization from alcohol. It formed long, colorless needles; m.p. 70-71.5°.

Analysis: Calc. for C_9H_8NBr: N, 6.67. Found: N, 6.64.

2-Bromo-5-nitro-m-xylene (C): The preparation of this compound presented several difficulties. Two methods appeared available. Conversion of 5-nitro-vic.-m-xylidine into the bromo-compound by a Sandmeyer reaction was hardly feasible, as the nitroxylidine could be prepared in but small quantities.[50] Nitra-

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[49] Fischer and Windaus, Ber., 33, 1967 (1900); Noelting, Braun, and Thesmar, op. cit.

[50] Ibbotson and Kenner, op. cit.

tion of 2-bromo-acetyl-asym.-m-xylidine, followed by elimination of the acetyl and amino-groups was found suitable for the preparation of large quantities, although somewhat arduous because of the numerous steps required. It was found that nitration in sulfuric acid solution leads to the 6-nitro-derivative, which yields the known compound 2-bromo-4-nitro-m-xylene after de-acetylation and de-amination. This is taken up later. On the other hand, nitration with fuming nitric acid yielded the 5-nitro-isomer, which leads to 2-bromo-5-nitro-m-xylene. The two different courses of nitration and the subsequent syntheses are indicated in Chart 1.

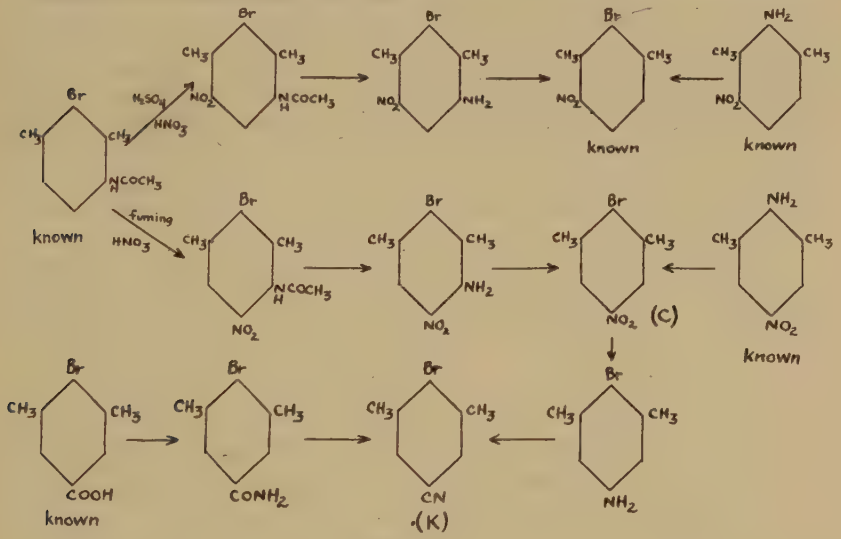

Chart 1

This chart illustrates the course of the synthetic work required in the preparation and proof of structure of some of the compounds described in the experimental part. Compounds previously described in the literature are so designated.

2-Bromo-5-nitro-acetyl-asym.-m-xylidine: Seventy grams of 2-bromo-acetyl-asym.-m-xylidine, prepared by the method of Noelting, Braun, and Thesmar,[51] were added in 10-gram quantities to a mixture of 350 c.c. of concentrated nitric acid and 250 c.c. of red fuming nitric acid at 5-10°. The temperature was then allowed to rise to 20°, where it was held for 15 minutes. The

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[51] Op. cit.

solution, now bubbling faintly, was poured into ice water. The precipitate was collected, washed with water, and recrystallized from alcohol. It was obtained in colorless needles; m. p. 191-192°. Yields ranged from 55-70% of the theoretical, being smaller for larger scale preparations. The preparation described above is an example of a large scale reaction.

Analysis: Calc. for $C_{10}H_{11}O_3N_2Br$: N, 9.76. Found: N, 9.76.

2-Bromo-5-nitro-asym.-m-xylidine: A mixture of 45.4 grams of 2-bromo-5-nitro-acetyl-asym.-m-xylidine and 350 grams of concentrated sulfuric acid was heated for ten minutes at 110-115°. The dark red solution was then poured on ice. A light orange precipitate was collected, washed with water, and recrystallized from alcohol. It formed orange-red needles which were only slightly soluble in cold alcohol; m.p. 141-142°. Yield, 37.5 grams (96.6% of theoretical).

Analysis: Calc. for $C_8H_9O_2N_2Br$: N, 11.44. Found: N, 11.60.

2-Bromo-5-nitro-m-xylene (C); from bromonitroxylidine: Thirty grams of 2-bromo-5-nitro-asym.-m-xylidine were suspended in 600 c.c. of alcohol containing 25 c.c. of concentrated sulfuric acid. It was diazotized at 10-13° with 18 grams of sodium nitrite in a little water. After four hours, the diazonium solution was carefully heated to boiling. Aldehyde and excess alcohol were removed by fractionation. The residue was diluted with water and steam distilled. The white solid material which passed over was collected, washed with water, and recrystallized from alcohol. It formed colorless needles; m.p. 102.5-103°. Yield, 18 grams (63.8% of theoretical).

Analysis: Calc. for $C_8H_8O_2NBr$: N, 6.09. Found: N, 6.14.

2-Bromo-5-nitro-m-xylene from 5-nitro-vic.-m-xylidine: A small quantity of 5-nitro-vic.-m-xylidine,[52] which was furnished by Dr. G. W. Wheland, was converted into the bromo-compound by a Sandmeyer reaction. The compound was isolated by steam distillation and, after one recrystallization from alcohol, it melted at 100-103°. Mixed melting points with the previous preparation were 100-103° and 100-102°. This synthesis of 2-bromo-5-nitro-m-xylene serves to prove its structure.

4-Bromo-3,5-dimethylbenzonitrile (K): The synthesis of this compound was achieved through two independent methods. The first

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[52] Ibbotson and Kenner, op. cit.

involved the reduction of 2-bromo-5-nitro-m-xylene (C) to the corresponding xylidine, which was then subjected to a Sandmeyer reaction. The second method was the conversion of p-bromomesitylenic acid into its amide and dehydration of this amide to the nitrile. These syntheses are indicated in Chart 1.

2-Bromo-sym.-m-xylidine: Ten grams of 2-bromo-5-nitro-m-xylene were suspended in 250 c.c. of alcohol and gradually added to a stirred solution of 36.5 grams of stannous chloride in 32.5 c.c. of concentrated hydrochloric acid. After standing for an hour, the alcohol was removed by distillation. The residue was made alkaline with aqueous sodium hydroxide and distilled in steam. A yellowish oil was obtained, which crystallized on standing for two days. It was dissolved in ether and recovered by evaporation of the ether solution. The oily residue was taken up in warm concentrated hydrochloric acid. The acid solution was boiled for a few minutes, quickly filtered, and allowed to cool. The precipitated amine hydrochloride was collected, suspended in water, and treated with an excess of sodium hydroxide solution. The white precipitate was collected and recrystallized from alcohol. It was obtained in colorless needles; m.p. 75.5-76°. Yield, 7 grams (80.5% of the theoretical).

Analysis: Calc. for $C_8H_{10}NBr$: N, 7.00. Found: N, 7.19.

4-Bromo-3,5-dimethylbenzonitrile (K) from bromoxylidine: Seven grams of 2-bromo-sym-m-xylidine were dissolved in 7 c.c. of concentrated sulfuric acid and 50 c.c. of water. It was diazotized at 0° with 3 grams of sodium nitrite. The neutralized diazonium solution was poured into an aqueous suspension of cuprous cyanide. The nitrile was obtained by steam distillation. It was purified by recrystallization from alcohol, then from high-boiling ligroin. It formed long, colorless prisms, up to one inch in length; m.p. 145°, with some sublimation. Yield, 400 milligrams of pure material.

Very little material was obtained during the steam distillation of the diazotization mixture. The yield could without doubt be improved considerably, but no more of the bromoxylidine was available.

Analysis: Calc. for C_9H_8NBr: C, 51.43; H, 3.84; N, 6.67. Found: C, 51.68; H, 3.73; N, 7.00.

4-Bromo-3,5-dimethylbenzamide: Two grams of p-bromomesitylenic

acid[53] were refluxed with an excess of thionyl chloride until all had dissolved. The cooled solution was carefully treated with strong ammonia. The white precipitate was collected, washed with water, and recrystallized from alcohol. The product was obtained as colorless needles and square platelets, with a pearly luster; m.p. 205-206°. Yield 1.5 grams.

Analysis: Calc. for $C_9H_{10}ONBr$: N, 6.15. Found: N, 6.40.

4-bromo-3,5-dimethylbenzonitrile (K) from amide: An intimate mixture of 1.5 grams of 4-bromo-3,5-dimethylbenzamide and 2 grams of phosphorus pentachloride were heated for 12 hours in a loosely stoppered flask. At the temperature of the steam bath, the mixture fused, but on cooling it solidified. The mixture was cautiously treated with water, then steam distilled. A white solid condensate was collected and recrystallized from alcohol. It formed colorless prisms; m.p. 144-145°. A mixed melting point with the product from 2-bromo-sym.-m-xylidine was 144°. Yield, 500 milligrams.

2-Bromo-6-nitro-acetyl-asym.-m-xylidine: While this compound was of no importance to our studies, it was obtained during early attempts to synthesize the 5-nitro-isomer. Its structure was proved by elimination of the acetyl group followed by de-amination to the known 2-bromo-4-nitro-m-xylene.

Two grams of 2-bromo-acetyl-asym.-m-xylidine were dissolved in 20 grams of concentrated sulfuric acid and treated with 0.75 gram of concentrated nitric acid below 15°. After 10 minutes, the solution was poured into ice water. The white precipitate was collected, washed with water, and recrystallized from dilute alcohol. It was obtained as small, white needles; m.p. 171-172°. Yields on 30-gram quantities of starting material were consistently over 90%.

Analysis: Calc. for $C_{10}H_{11}O_3N_2Br$: N, 9.76. Found: N, 9.83.

2-Bromo-6-nitro-asym.-m-xylidine: Thirty grams of 2-bromo-6-nitro-acetyl-asym.-m-xylidine were refluxed with 50% sulfuric acid until all had dissolved. The solution was poured into cold water and neutralized with ammonia water. The yellow precipitate was collected, washed with water and recrystallized from alcohol, after decolorization with Norite. It formed yellow needles; m.p. 129-130°, with extensive sublimation.

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[53] Fittig and Störer, Ann., 147, 1 (1868).

Analysis; Calc. for $C_8H_9O_2N_2Br$: N, 11.44. Found: N, 11.67.

The strudture was proved by conversion into 2-bromo-4-nitro-m-xylene. This was accomplished by the method employed for de-amination of 2-bromo-5-nitro-asym.-m-xylidine as described above, except that the temperature of diazotization was 5-7°. After several recrystallizations and decolorizations, the product, which had been isolated by steam distillation, was obtained in colorless needles of waxy, plastic consistency; m.p. 56.5-58°. A mixed melting point with 2-bromo-4-nitro-m-xylene obtained from 4-nitro-vic.-m-xylidine by the method of Noelting, Braun, and Thesmar[54] was 56-57°. M.p. lit. 57-58°. The compound as described by these authors is light yellow. This is probably due to an impurity which comes from steam distillation of a deep red diazonium solution.

III

Since the reaction of piperidine with cyano-aryl halides had not been reported, it was necessary to investigate the reaction to determine whether it was suitable for a kinetic study. The particular nitrile chosen was p-bromo-benzonitrile, because of its availability and comparatively high reactivity. It was found that p-piperidinobenzonitrile was the sole product of the reaction aside from piperidine hydrobromide. This nitrile was hydrolyzed to p-piperidinobenzoic acid. Some difficulty was encountered here in that the melting point of this acid had been incorrectly reported by Scholz and Wassermann.[55] However, a check on the work of these authors disclosed the error. This is reported more fully below. The course of the synthesis and proof of structure is illustrated in Chart 2.

p-Piperidinobenzonitrile: Ten grams of p-bromobenzonitrile were refluxed with 20 c.c. of piperidine for 8 hours. The solution was poured into water and just neutralized with hydrochloric acid. It was then made very slightly alkaline with sodium carbonate. A heavy oil separated and solidified on long standing. This solid was dissolved in benzene and the solution extracted with 20% hydrochloric acid. The benzene solution was dried and evaporated to dryness. The residue (3.10 grams, 31%

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[54] Op. cit.

[55] Scholz and Wassermann, Ber., 40, 852 (1907).

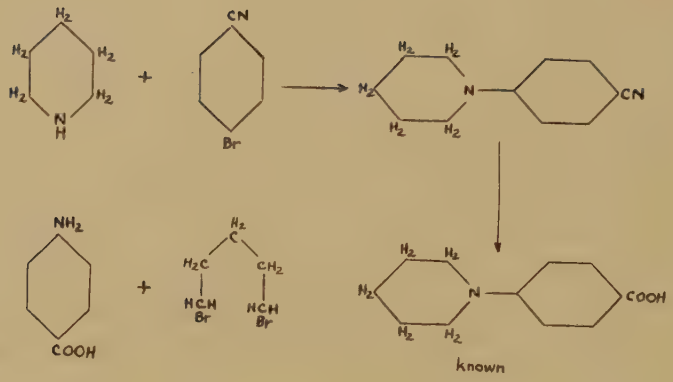

Chart 2

This chart illustrates the synthesis and proof of structure of p-piperidinobenzonitrile.

of the original bromobenzonitrile, assuming that this residue was unchanged material) was taken up in a small amount of alcohol, diluted with water, and steam distilled. It was further purified by recrystallization from dilute alcohol. The purified material (2.8 grams) melted at 110-112°. A mixed melting point with a known sample of p-bromobenzonitrile (m.p. 113°) was 110-111°.

The hydrochloric acid extracts were neutralized with ammonia water. A yellow precipitate was collected and washed with water. The filtrate yielded a further small quantity of material upon extraction with ether. The combined weight of this material was 6.75 grams (66%, assuming that it was p-piperidinobenzonitrile). After several recrystallizations, first from 95% alcohol, then from more dilute alcohol, it was obtained in light yellow leaflets; m.p. 55°. The weight of pure material was 5.8 grams. Thus 97% of the starting material was recovered as reaction product or unchanged material. The purified materials accounted for 84% of the original p-bromobenzonitrile.

The molecular weight was determined cryoscopically in benzene solution. Calc. mol. wt. for $C_{12}H_{14}N_2$: 186. Found: 182,

188.

Analysis: Calc. for $C_{12}H_{14}N_2$: N, 15.06. Found: N, 15.04.

p-Piperidinobenzoic acid: One gram of p-piperidino-benzonitrile was refluxed with 40 c.c. of 20% hydrochloric acid for 2 1/2 hours. After cooling, the clear solution was neutralized with dilute aqueous potassium hydroxide, litmus being used as the indicator. The almost white precipitate was collected, washed with water, dissolved in alcohol, decolorized with Norite, and recrystallized. It formed white leaflets; m.p. 224-224.5°.

Analysis: Calc for $C_{12}H_{15}O_2N$: N, 6.83. Found: N, 6.93.

The melting point of this compound as reported by Scholz and Wassermann[56] is 188°. These investigators synthesized the compound by treating p-aminobenzoic acid with pentamethylene bromide. In view of the scanty directions given, it was not possible to duplicate their work exactly. The followed procedure was employed.

Five grams of pentamethylene bromide and 10.5 grams of p-aminobenzoic acid were refluxed in 30 c.c. of methyl alcohol for 48 hours. After prolonged cooling, about 2 grams of a white crystalline precipitate deposited. After several recrystallizations from dilute alcohol, the material melted at 220-223°. Mixed melting points with the hydrolysis product of the nitrile were 220-222° and 221-224°. The identity of the two preparations is therefore established with reasonable certainty. It is suggested that since Scholz and Wassermann also report the melting point of the m-piperidinobenzoic acid as 227° (which is close to the temperature observed here for the para-acid), a confusion in the report of the melting points of the two acids has occurred.

IV

The solvents, standard solutions, and technique of the kinetic measurements are described in the following paragraphs.

Benzene: Thiophene-free benzene was fractionated from over sodium and stored over sodium wire. B.p. 79.5-80°.

Ethylbenzene: The Eastman product was dried, fractionated and stored as described for benzene. B.p. 134-135°/753mm.

Piperidine: Eastman's best grade piperidine was dried, fractionated,

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[56] Op. cit.

and stored as described for benzene. B.p. 105-106°. This preparation gave the same results as piperidine prepared from benzoylpiperidine.[57]

Dioxane: Commercial dioxane was purified by the method of Eitel and Lock,[58] and gave only a faint test for halogen after four hours' boiling with aqueous sodium hydroxide.

Standard sodium hydroxide solution: Mallinckrodt sodium hydroxide of low chlorine content (assay, 0.001% Cl, 67-70% NaOH) was used in the preparation of the standard base solution. Forty-three and a half grams were dissolved in as little distilled water as possible, filtered from precipitated carbonates and silicates, and diluted to 1100 c.c. with distilled water which had been freshly boiled. To this solution were added 1300 c.c. of dry dioxane. The solution was titrated against standard potassium acid phthalate and its normality was found to be 0.2957.

Kinetic measurements employing piperidine: The procedure was essentially the same as that used by Salkind, by Sandin and Liskear[59] and by McLeish and Campbell.[60]

The nitrobromo- or cyanobromo-compound (approximately 0.0018 mole) and piperidine (approximately 0.0510 mole) were weighed out and transferred to a 100-c.c. round bottom flask, which could be attached to a reflux condenser by means of a ground glass joint. Ten c.c. of benzene or ethylbenzene[61] were pipetted into the flask and the mixture gently refluxed for eight hours. At the end of this time, the contents of the flask were rapidly cooled by an external cold water bath, while 15 c.c. of water were added through the condenser. The benzene or ethylbenzene layer was separated from the aqueous layer and washed several times with water. The combined aqueous extracts were analyzed for halogen by the Volhard method. Tenth-normal solutions of silver nitrate and potassium thiocyanate were de-

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[57] Org. Syn., Coll. Vol., p. 95.

[58] Eitel and Lock, Monatsh., 72, 392 (1939).

[59] Op. cit. [60] Op. cit.

[61] Benzene was employed in the determinations with nitroaryl halides. For the bromo-nitriles, a higher temperature was necessary to accelerate the reaction, and ethylbenzene proved to be a satisfactory solvent for this purpose.

livered from semimicro-burettes.

For the benzene solutions, a negligible blank was found. For the ethylbenzene solutions, a blank of 0.0016 milliequivalents was found and the percentage reaction was corrected for this amount.

Kinetic measurements employing NaOH solutions: The nitroaryl halide (approximately 0.0018 mole) was refluxed for 24 or 48 hours with 65 c.c. of standard base solution, which was delivered from a burette. After this time, the cooled solution was treated with 25 c.c. of benzene, added through the condenser. The aqueous layer was separated and the benzene solution extracted several times with water. The combined aqueous extracts were analyzed by the Volhard method.

A blank of 0.0168 milli-equivalents was found for the 24-hour period and 0.0221 milli-equivalents for the 48-hour period. The analytical figures were corrected by these amounts.

These determinations were rendered difficult by the separation of much siliceous material, resulting from the reaction of the hot sodium hydroxide solution with the glass reaction vessel. However, a blank determination on a quantity of potassium bromide, approximately the same in bromide content as the final reaction mixtures, gave analyses correct to 1%. The loss of sodium hydroxide by reaction with the glass vessel is probably a constant for each period of heating.

SUMMARY

1. A review of physical and chemical effects of ortho-substituents has been presented.

2. The inductive and steric effects of methyl groups ortho to nitro-, bromo-, and cyanogroups in nitro-aryl and cyano-aryl bromide have been investigated. It was found that methyl-groups ortho to the nitro-group have a definite effect in hindering the resonance of the nitro-compound. The effect of methyl groups ortho to a bromo-group in both classes of compounds is a combination of inductive and steric effects, the latter in the usual sense of the term. The influence of methyl groups ortho to the nitrile groups in ortho- and para-bromo-nitriles is chiefly inductive in nature.

3. The reaction of piperidine with p-bromobenzonitrile

has been investigated for the first time.

4. The synthesis and physical properties of eleven new compounds have been reported.

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